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P53 marker expression in epithelial ovarian tumours in a centre in Nigeria – a descriptive study

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Abstract

Background p53 is a tumor suppressor gene. p53 expression in epithelial ovarian tumors (EOTs) is correlated with their biological behavior and predicts patient overall survival. However, there is a dearth of knowledge regarding p53 expression in these tumors among women from southwest Nigeria. Our study aimed to determine the patterns of p53 expression in various types of epithelial ovarian tumours.

Methods We conducted a retrospective study of epithelial ovarian tumours. We retrieved formalin-fixed, paraffin-embedded (FFPE) tissue blocks of previously diagnosed epithelial tumors from the departmental archive. We performed immunohistochemical analysis using p53 antibodies. We scored the expression and staining intensity of p53 as follows: negative (0), focal/weakly positive (1 +), and diffuse/strongly positive (2 +) on the basis of the recommended Cytomation scoring system.

Results The spectrum of p53 expression in the 51 histologically diagnosed cases revealed that 29 cases had no expression, consisting of 21 benign EOTs, two borderline EOTs, and six malignant EOTs. Nine cases exhibited wild-type expression, including six serous carcinomas, two mucinous carcinomas, and one signet ring cell carcinoma. p53 overexpression was observed in 13 patients overall, with 12 having serous carcinomas and one having endometrioid carcinoma. Among the 21 serous carcinoma patients, 28.6% (6 patients) presented with wild-type p53 expression, 57.1% (12 patients) presented with p53 overexpression, and 14.3% (three patients) presented negative p53 expression. There was a significant association between p53 expression and the histological grade of serous carcinoma.

Conclusion Most epithelial ovarian carcinomas in our hospital are high grade, with many serous carcinomas showing either p53 overexpression or loss of expression. This may contribute to the poor patient survival rate.

Keywords EOTs, Epithelial ovarian tumours, p53, Immunohistochemistry, Serous carcinoma

Introduction

p53 is a tumor suppressor gene located on chromosome 17p13 that encodes a 53 kDa protein. It is often referred to as the 'guardian of the genome' because it facilitates the repair of damaged DNA before proceeding with cell division [1]. p53 induces cell cycle arrest to allow time for DNA repair or triggers apoptosis through activation of the BAX gene if the damage is irreparable.

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Epithelial ovarian tumors (EOTs) have recently been studied via molecular methods, enabling more detailed characterization and improved prognostication of these tumors [2–5]. Molecular characterization has enhanced the understanding of the molecular pathogenesis of ovarian carcinomas, enabling pathologists to play a crucial role within the oncology team by providing more precise diagnoses that significantly contribute to patient treatment [6–8].

There has been a significant shift from traditional morphology-based diagnoses of ovarian carcinomas toward comprehensive molecular characterization. As a result, pathologists, through more advanced examinations of ovarian samples, have linked molecular subtypes to clinical presentations. Some studies have reported worse survival outcomes in patients with p53 overexpression [9, 10]. The molecular classification of ovarian carcinomas into distinct subgroups has also provided insights into the specific genes driving each subgroup, thereby highlighting the heterogeneity of epithelial carcinomas [3, 11, 12].

Missense and null mutations in the p53 gene have been associated with ovarian cancer. P53 expression can be readily assessed using immunohistochemistry. The morphological and molecular features of epithelial ovarian carcinomas should be evaluated for each patient to ensure a personalized and targeted approach to patient management [13, 14]. There is a dearth of studies on p53 immunohistochemistry of ovarian cancers in southwest Nigeria. This study aimed to determine the patterns of p53 expression in various types of epithelial ovarian tumors.

Materials and methods

Study design

We conducted a retrospective study of epithelial ovarian tumors (EOTs) diagnosed at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, over a ten-year period from January 2005 to December 2014. We retrieved formalin-fixed, paraffin-embedded (FFPE) tissue blocks of previously diagnosed epithelial tumors from the departmental archive for review. We performed immunohistochemical analysis using p53 antibodies.

We included ovarian cancer samples from patients who underwent total abdominal hysterectomy with salpingo-oophorectomy, bilateral or unilateral salpingo-oophorectomy, and ovarian cystectomy. We excluded cases of nonepithelial primary ovarian cancer, metastatic cancers involving the ovary, and primary ovarian epithelial neoplasms where slide sections were unsuitable or where tissue blocks were unavailable.

Tissue preparation

We remounted the retrieved tissue blocks and manually sectioned them into 2–3 μm thick slices via a microtome. We floated these sections in a warm-water bath and mounted them onto adhesive-coated Superfrost Plus slides. We then placed the slides on a warmer set at 60 °C for 1 h. From each block, we prepared seven slides: one for routine hematoxylin and eosin (H&E) staining and six for immunohistochemical staining.

We reviewed the newly prepared H&E slides and classified and graded the tumors on the basis of the WHO classification of EOTs, considering both their histological cell type and behavior. We graded the tumors via the WHO/Universal/Shimizu criteria and compared them with the MD Anderson two-tier grading system.

Immunohistochemistry protocol

We subjected all the tissue sections to immunohistochemical analysis regardless of the initial H&E assessment. We used a known positive serous carcinoma of the ovary as an external control.

Deparaffinization

We deparaffinized the slides by immersing them in two changes of xylene for 5 min each. We then rehydrated the slides with three changes of 100% ethanol for 3 min each, followed by 95% and 70% ethanol for 1 min each. Afterward, we rinsed the slides in phosphate-buffered saline (PBS).

Antigen retrieval

We placed the slides in heat-induced epitope retrieval (HIER) citrate buffer, diluted them 1:10 with distilled water, and incubated them in a microwave at 90 °C for 1 h. We then transferred the slides to fresh citrate buffer and allowed them to cool for 20 min before they were rinsed with PBS. We processed positive and negative controls alongside the experimental slides to ensure valid results.

Peroxidase blocking

We placed the slides in a humid chamber and marked the tissue periphery with a hydrophobic pen. We applied a 3% hydrogen peroxide solution to each tissue section for 10 min to block endogenous peroxidase activity, followed by rinsing in PBS (0.1%).

Immunoperoxidase staining

We carried out immunohistochemical staining via the Leica BOND™ system with a ready-to-use p53 (DO-7) primary antibody (catalogue no. PA0057) and associated detection kits. We incubated the samples with

40–130 µl of appropriately diluted Leica mouse primary antibody for 1 h, depending on the tissue surface area. Afterward, we incubated the slides with an undiluted horseradish peroxidase (HRP)-conjugated anti-mouse secondary antibody for 30 min. After rinsing in PBS, we applied a substrate-chromogen (diaminobenzidine [DAB]) solution and incubated the slides for 15 min. We counterstained the slides by immersing them in aqueous hematoxylin, followed by rinsing in distilled water for 3 min.

We then dehydrated the tissue sections through a series of graded alcohols (70%, 95%, and 100%) and cleared them with xylene. Mounting medium was added, and a coverslip was placed.

Slide review

To assess the quality of the staining process, we employed a known positive serous carcinoma of the ovary as an external control. Additionally, the quality of the retrieved tissue blocks was evaluated by examining the expected weak nuclear positivity of lymphocytes within the tissue sections.

To minimize bias, two pathologists independently reviewed all slides without knowledge of the initial histologic diagnosis. In cases of disagreement, a consensus was reached through joint discussion. We scored the expression and staining intensity of p53 as follows: negative (0), focal/weakly positive (1+), and diffuse/strongly positive (2+) on the basis of the recommended Cytomation scoring system.

Intensity of p53 staining

	Negative	Wild-Type Expression	Overexpression
Score	0	1+	2+
Positive Cells	<10%	10–50%	>50%

Statistical analysis

Statistical analysis was performed using SPSS version 20. To assess the association between categorical variables, the chi-square test of independence was used. Data visualization was performed using the ggplot2 package in R to create informative charts.

Results

A total of 125 ovarian tumor cases were reported during the study period. Of these, 53 were surface epithelial tumors, with 51 cases suitable for analysis. Overall, 21 patients (41.2%) had benign neoplasms, 2 patients (3.9%) had borderline neoplasms, and 28 patients (54.9%) had malignant neoplasms.

Thirty-eight patients (74.5%) had serous tumors, 8 patients (15.7%) had mucinous tumors, and 3 patients (5.9%) had Brenner tumors. Signet ring cell carcinoma and endometrioid carcinoma each accounted for 1 case (2%). No case of clear cell carcinoma was recorded. Among the 28 patients with malignant EOTs, 21 (75%) had serous cystadenocarcinomas, and 5 (17.9%) had mucinous cystadenocarcinomas.

Among the 51 cases, 29 (56.9%) were negative for p53 expression, 9 (17.6%) were wild-type, and 13 (25.5%) were positive for the p53 marker.

The spectrum of p53 expression in the 51 histologically diagnosed cases revealed that 29 cases had negative expression, consisting of 21 benign EOTs, 2 borderline EOTs, and 6 malignant EOTs. Nine cases exhibited wild-type expression, including 6 serous carcinomas, 2 mucinous carcinomas, and 1 signet ring cell carcinoma. P53 overexpression was observed in 13 patients overall, with 12 having serous carcinomas and 1 having endometrioid carcinoma. Figure 1 summarises the pattern of p53 expression across various ovarian tumors. Figure 2 illustrates the frequency distribution of the most common ovarian cancer types.

Among the 21 serous carcinoma patients, 28.6% (6 patients) presented with wild-type p53 expression, 57.1% (12 patients) presented with p53 overexpression, and 14.3% (3 patients) presented negative p53 expression.

Among the 5 patients with mucinous carcinoma, 40% (2 patients) had wild-type p53 expression, whereas 60% (3 patients) had negative p53 expression.

We conducted a Fisher's exact test to assess the association between P53 expression and serous carcinoma in epithelial ovarian tumors. The test yielded a chi-square statistic of 27.05 with a p-value < 0.001, indicating a significant association between the two variables. We calculated Cramer's V effect size to quantify the strength of this association, resulting in a value of 0.721, which is considered large. We estimated a 95% confidence interval for this effect size, based on 1000 bootstrap samples, to be 0.53 to 0.89. Figure 3 presents a bar chart visualizing the pattern of p53 expression in serous carcinoma relative to other tumor types.

A binary logistic regression was conducted to evaluate the effect of P53 expression patterns on the likelihood of an ovarian tumor being classified as a serous carcinoma. Wild-type and negative expression patterns were used as the reference category. The model was statistically significant ($\chi^2 = 20.45$, $p < 0.001$, Omnibus Tests of Model Coefficients), indicating that P53 overexpression effectively distinguished serous carcinomas from other epithelial ovarian tumors. The model accounted for 44.5% of the

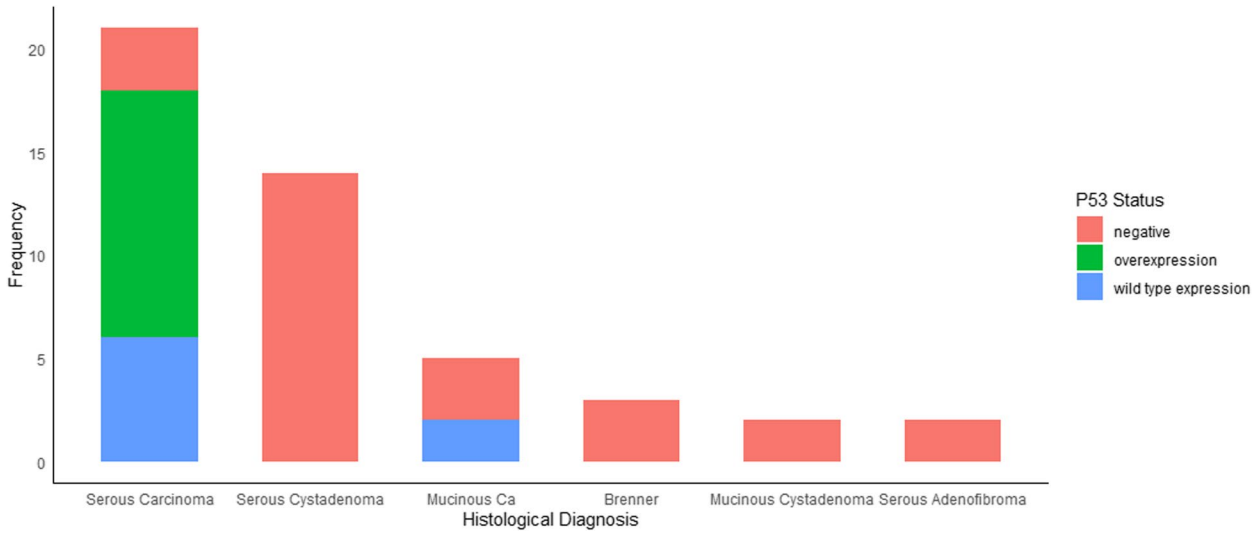

Fig. 1 P53 expression in the most frequent epithelial ovarian tumors. Figure 1 illustrates P53 expression across the six most common epithelial ovarian tumors. Serous tumors were observed to be relatively more common than other types. Notably, both wild-type and overexpression of P53 were identified in serous carcinoma, while no P53 expression was detected in cases of serous cystadenoma

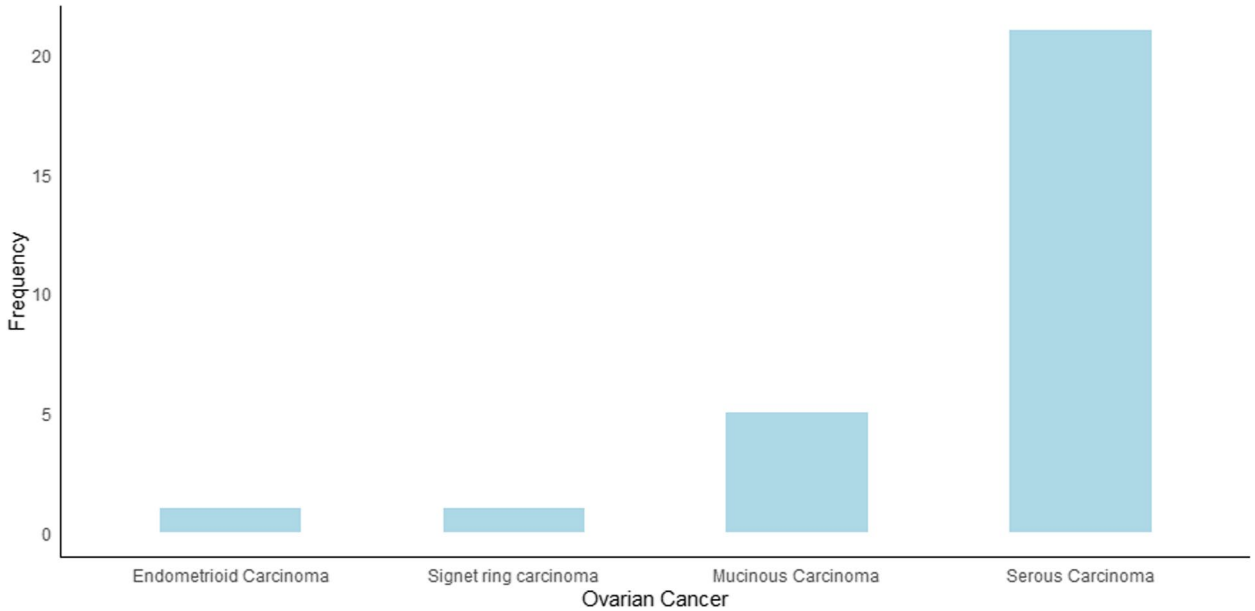

Fig. 2 The most frequent epithelial ovarian cancers. Figure 2 highlights that serous carcinomas represent a significant proportion of epithelial ovarian cancers

variance in the outcome (Nagelkerke R^2) and correctly classified 80.4% of cases.

P53 overexpression was significantly associated with serous carcinoma, with an odds ratio of 38.7 (95% CI: 4.403–339.589). While this suggests a strong association, the wide confidence interval indicates some imprecision in the estimate, likely due to a limited sample size or variability in the data. Further research with larger sample sizes may help to refine this estimate. Figure 4 illustrates the varied expression patterns of p53 in selected epithelial ovarian tumors.

Discussion

Our study underscores the diagnostic value of P53 immunohistochemistry in identifying serous ovarian cancers at our center. P53 overexpression is strongly correlated with

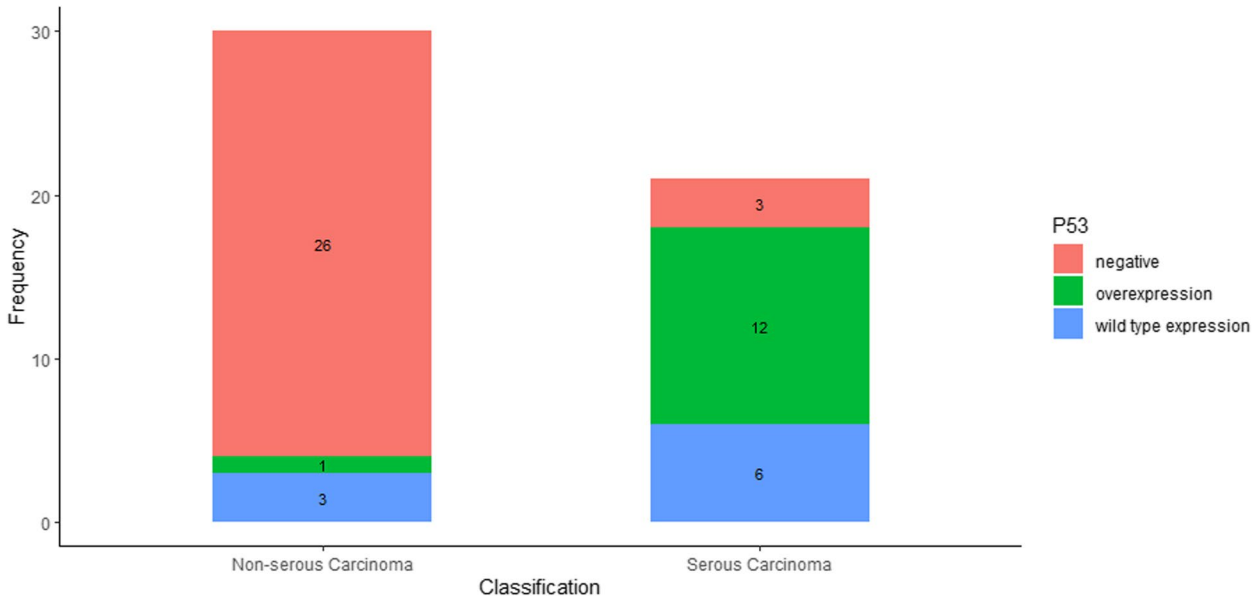

Fig. 3 P53 expression in serous carcinoma and other epithelial ovarian tumours. Figure 3 compares P53 expression in serous carcinoma with other epithelial ovarian tumors (both benign and malignant non-serous types), demonstrating a higher proportion of overexpression in serous carcinoma

serous ovarian carcinomas, making it a valuable tool for distinguishing these malignancies from benign serous tumors and other types of epithelial ovarian cancers. Notably, ovarian cancers at our center frequently present at advanced stages, with some patients manifesting metastatic symptoms prior to the identification of the primary tumor. Furthermore, P53 immunohistochemistry demonstrates potential for diagnosing serous carcinomas at metastatic sites, thereby enhancing its clinical utility.

Numerous studies from various regions of the world have reported findings consistent with ours. In Nigeria, research has documented a higher rate of P53 expression in ovarian serous carcinomas compared to other epithelial ovarian tumors [15]. Similar patterns have been observed in studies conducted in other African countries [16–18]. Additionally, research from other continents has consistently demonstrated elevated levels of P53 expression in serous ovarian carcinomas, highlighting its global significance as a hallmark feature of this tumor subtype [19–22].

Studies have investigated the prognostic significance of p53 dysfunction and its patterns in ovarian carcinomas, particularly the relationship between p53 overexpression and mutations, as well as their impact on overall survival [23]. The level of p53 expression in epithelial ovarian tumors (EOTs) may help distinguish high-grade from low-grade tumors and influence tumor aggressiveness. Several studies have noted poorer survival outcomes in patients with p53 overexpression [24]. The molecular events driving p53 expression patterns may occur early or late in tumorigenesis, underscoring their potential role in disease progression.

In this study, p53 overexpression was observed in 25.5% of epithelial ovarian tumor (EOT) cases, specifically within high-grade subtypes. Among these, twelve cases were diagnosed as serous carcinomas, and one endometrioid carcinoma, both recognized as high-grade carcinoma categories. This pattern of p53 expression aligns with the findings of several other studies, which consistently report a strong association between p53 overexpression and high-grade ovarian carcinomas, underscoring its potential role in the pathogenesis and aggressive behavior of these malignancies. Importantly, our results further illustrate that benign and borderline EOTs do not typically exhibit p53 overexpression, suggesting that p53 may not play a significant role in the development of lower-grade tumors. These findings reinforce the hypothesis that p53 mutation-driven overexpression is a hallmark of aggressive ovarian tumor phenotypes, potentially contributing to their distinctive clinical behaviors and poorer prognoses, as extensively documented in prior research [15, 25–29].

Nine malignant epithelial ovarian tumors (EOTs) demonstrated wild-type p53 expression, including low-grade serous and mucinous carcinomas. Previous studies have similarly reported that serous and mucinous carcinomas with wild-type p53 expression are typically low-grade [30–32]. We also identified a single case of signet ring carcinoma with wild-type p53 expression, which we believe is likely metastatic rather than a primary ovarian

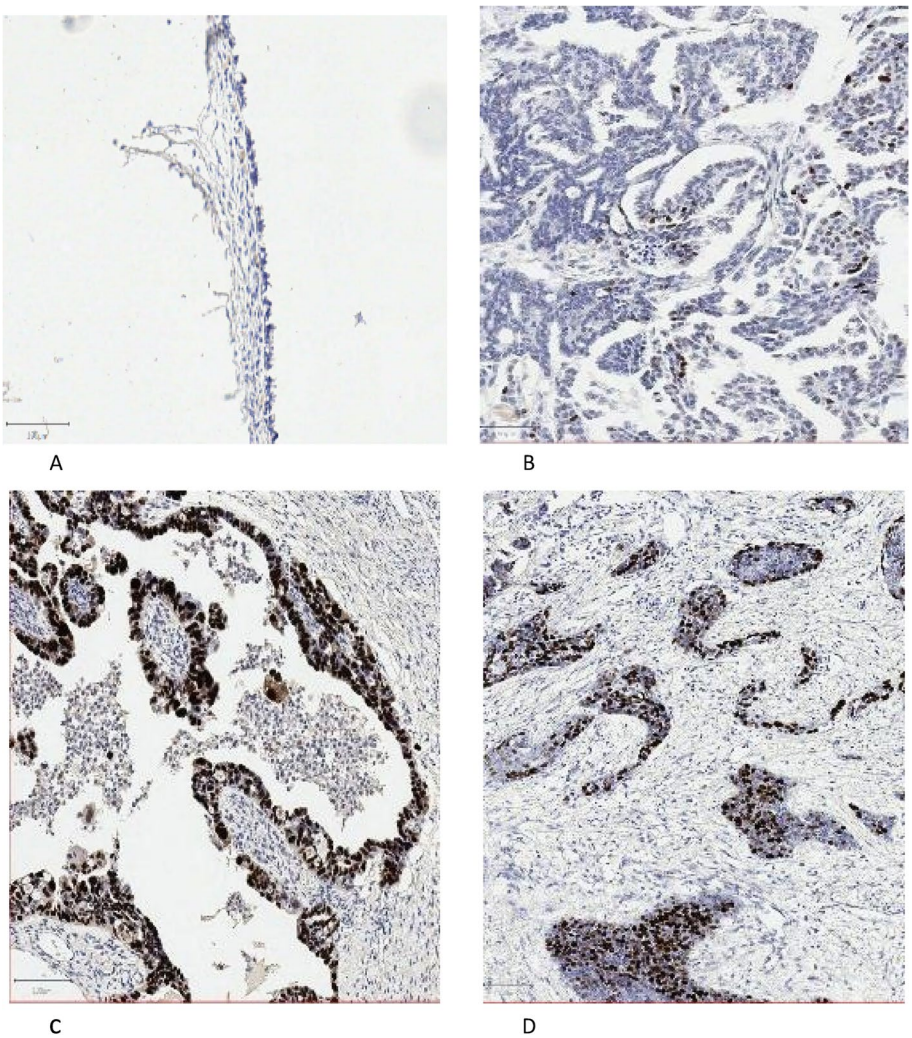

Fig. 4 Epithelial ovarian tumors (EOTs). Figure 4 shows Negative P53 expression in serous cystadenoma x100x (**A**); wild-type P53 expression in LGSC x200 (**B**); strong and diffuse P53 overexpression in HGSC x100 (**C**); strong and diffuse P53 overexpression in endometrioid carcinoma X100 (**D**)

malignancy. The clinical behavior and prognostic implications of wild-type p53 expression have been inconsistently reported. While wild-type p53 is more commonly observed in low-grade tumors, some studies associate it with favorable outcomes, whereas others link it to poorer prognoses [33, 33, 34].

Ovarian carcinomas are classified into five distinct grade groups on the basis of histopathology and molecular genetic alterations: high-grade serous carcinoma (HGSC), endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma and low-grade serous carcinoma (LGSC) according to studies by J. Prat [11]. In this study, 44.4% of the patients had serous carcinoma with p53 overexpression (HGSC), and 22.2% of the patients had serous carcinoma with wild-type p53 expression (LGSC). Hence, most of the ovarian carcinomas seen in our center are high-grade serous carcinomas. This may partly explain the overall aggressive nature and poor prognosis of most ovarian cancers in our region of the world. The already well-established fact of late presentation at the hospital and more advanced stage of most of the ovarian cancers at diagnosis are other contributors to poor ovarian cancer patient outcome.

Mutations causing loss of wild-type p53 function due to either gain of abnormal function of mutant p53 or absent or low mutant p53 are usually associated with the aggressive behaviour. It is generally accepted that both high and low, or entirely absent, p53 expression

correlates significantly with mutant p53. Expression levels between these two extremes are thought to represent wild-type p53 [27, 35]. Three (11.1%) of the patients had serous carcinoma with no P53 expression. These three cases may be properly categorized as HGSC if p53 sequencing is performed to identify the type of mutant p53. This may increase the number of HGSCs by 11.1% to 55.5%.

Abnormal p53 expression (overexpression or negative expression) is significantly associated with high-grade serous carcinoma in epithelial ovarian tumors and hence can be utilized in our center to identify epithelial ovarian cancers with a more aggressive clinical course and poorer prognosis. This will enable us to provide our gynaecologists with more details that will impact management. We also believe that p53 immunostaining may help identify aggressive lesions in pyknotic epithelial cells, especially following poor fixation. Using nuclear features to determine histological grade may not be the best for poorly fixed samples.

Our study is limited by the lack of detailed tumor staging information, which could have provided valuable insights into the correlation between p53 expression patterns and prognosis. This could have helped to clarify previous reports that have found little or no association between P53 expression and pathologic stage of the disease or survival [16, 21]. Additionally, we were unable to conduct advanced mutational analysis using PCR or genetic sequencing. Our study is further limited by the use of archival tissue blocks, which may have reduced antigen preservation compared to fresh or recently harvested tissues. A prospective study incorporating more comprehensive staging data, longer follow-up periods, and advanced molecular techniques would be worthwhile to further explore the significance of our findings. The relatively small size of our data and its cross-sectional nature are limitations to inference that could be deduced from our study. We need to conduct a larger study to include more data and follow-up patients to study the morbidity and mortality of this disease.

Conclusion

Most epithelial ovarian carcinomas at our hospital are high-grade, with many serous carcinomas exhibiting abnormal p53 expression, either overexpression or loss of expression. This may contribute to the poor patient survival rate. P53 immunohistochemistry is crucial in the evaluation of epithelial ovarian cancers, enabling the management team to predict more accurately and classify patients into appropriate treatment categories.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-024-03487-0.

Supplementary Material 1.

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Authors' contributions

An.O.A. was responsible for the study's design and conceptualization, drafted the original manuscript, developed the methodology, performed the data analysis, and contributed to interpretation and discussion. O.O.O. contributed to the methodology, data analysis, and discussion. At.O.A. participated in developing the methodology and data analysis. G.O.O. and A.O.K. supervised the study, reviewed the original draft, contributed to the methodology and data analysis, and approved the final version of the manuscript.

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Data availability

Data is provided as a supplementary information file.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical and Research Committee of the Obafemi Awolowo University Teaching Hospitals Complex. Informed consent for this study was waived in accordance with the guidelines of the Ethical and Research Committee of the Obafemi Awolowo University Teaching Hospitals Complex.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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